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Two Simple Rules for Improving the Accuracy of Empiric Treatment of Multidrug-Resistant Urinary Tract Infections

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The emergence of multidrug-resistant (MDR) uropathogens is making the treatment of urinary tract infections (UTIs) more challenging. We sought to evaluate the accuracy of empiric therapy for MDR UTIs and the utility of prior culture data in improving the accuracy of the therapy chosen. The electronic health records from three U.S. Department of Veterans Affairs facilities were retrospectively reviewed for the treatments used for MDR UTIs over 4 years. An MDR UTI was defined as an infection caused by a uropathogen resistant to three or more classes of drugs and identified by a clinician to require therapy. Previous data on culture results, antimicrobial use, and outcomes were captured from records from inpatient and outpatient settings. Among 126 patient episodes of MDR UTIs, the choices of empiric therapy against the index pathogen were accurate in 66 (52%) episodes. For the 95 patient episodes for which prior microbiologic data were available, when empiric therapy was concordant with the prior microbiologic data, the rate of accuracy of the treatment against the uropathogen improved from 32% to 76% (odds ratio, 6.9; 95% confidence interval, 2.7 to 17.1; $P < 0.001$). Genitourinary tract (GU)-directed agents (nitrofurantoin or sulfa agents) were equally as likely as broad-spectrum agents to be accurate ($P = 0.3$). Choosing an agent concordant with previous microbiologic data significantly increased the chance of accuracy of therapy for MDR UTIs, even if the previous uropathogen was a different species. Also, GU-directed or broad-spectrum therapy choices were equally likely to be accurate. The accuracy of empiric therapy could be improved by the use of these simple rules.

The incidence of infections caused by multidrug-resistant (MDR) Gram-negative bacterial uropathogens is increasing among both hospitalized patients and patients in the community (1, 2). The emergence of these pathogens creates challenges for physicians when choosing empiric treatment, as therapeutic options are often limited. Current guidelines for the treatment of urinary tract infections (UTIs) from the Infectious Diseases Society of America (IDSA) recommend that antimicrobial resistance rates be considered and that patient risk factors be taken into account (3). However, with rates of extended-spectrum beta-lactamase (ESBL) production among uropathogens approaching 10% (4, 5), additional strategies for selecting an accurate antimicrobial agent are needed.

Studies suggest that empiric treatment for patients with bacteremia caused by ESBL-producing strains accurately covers the pathogen in only half of all cases (6, 7). Inaccurate therapy has been associated with both increased morbidity and increased mortality (6–8). In addition, use of inaccurate therapy for MDR UTIs can increase both the cost of care and the length of stay for hospitalized patients (9). As urinary sources are one of the most common sources of bacteremia caused by Gram-negative bacteria and treatment for UTIs is usually initiated prior to the availability of microbiologic data, it is important to optimize decision making for the initial choice of antimicrobial therapy. Although previous studies have examined the rates of inaccurate therapy for MDR UTIs, few have evaluated strategies for improving accuracy (9–11).

The purpose of this study was to evaluate the accuracy, defined as the *in vitro* activity of empiric therapy for MDR UTIs, and to identify factors that might improve accuracy.

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MATERIALS AND METHODS

We utilized a database with data on infections caused by multidrug-resistant Gram-negative bacterial uropathogens collected at three U.S. Department of Veterans Affairs (VA) facilities over 4 years (2010 through 2013) and extracted the data for a subset of patient episodes that met our definition of an MDR UTI (12). An MDR UTI was defined as a clinician-identified infection requiring therapy caused by a uropathogen resistant to three or more classes of drugs. A retrospective review of the electronic health record was performed to determine the empiric treatment regimens used and previous microbiologic data. Data were available from the inpatient and outpatient settings for the local facility as well as the national VA system. This study was approved by the VA Boston Healthcare System Institutional Review Board.

Antibiotic classifications were divided into genitourinary tract (GU)-directed agents (which included nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin, the three antimicrobials recommended by the IDSA for the treatment of cystitis), broad-spectrum agents (which included carbapenems and antipseudomonal beta-lactams), and other agents (which included fluoroquinolones, aminoglycosides, and all other nonpseudomonal beta-lactams).

Empiric therapy was considered concordant with the previous microbiologic data if it was active against all isolated Gram-negative bacterial

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TABLE 1 Factors associated with accurate empiric therapy for MDR UTIs[a]

Factor	No. (%) of UTI episodes		Univariate OR (95% CI)	*P* value
	Total ($n = 126$)	With accurate therapy		
No prior data	31 (25)	12 (39)		
Therapy concordant with prior data	52 (41)	40 (77)	6.9 (2.7–17.1)	<0.05[b]
Therapy disconcordant with prior data	43 (34)	14 (33)		
Therapy concordant and same species	40 (32)	35 (88)	9.8 (2.2–43.1)	<0.05[b]
Therapy concordant and different species	12 (10)	5 (42)		
Therapy concordant and data within 6 mo	41 (33)	30 (73)	0.3 (0.03–2.4)	0.3
Therapy concordant and data within 2 yr	11 (9)	10 (91)		
Treatment with broad-spectrum antibiotics	33 (26)	26 (78)	1.8 (0.6–5.4)	0.3
Treatment with GU-directed antibiotics	26 (31)	39 (69)		

[a] Abbreviations: OR, odds ratio; CI, confidence interval; GU, GU directed.
[b] Statistically significant difference.

pathogens within 6 months of the index episode. For patients without available microbiologic data within 6 months, microbiologic data from a 2-year time frame from the date of the index patient episode were used to ascertain concordance. The difference in concordance rates between these two time frames was calculated. When there were numerous previous cultures, the culture with a profile with the most resistance was used to determine the classification of concordant treatment. Patterns of antimicrobial use were calculated and compared using JMP statistical software (SAS, Cary, NC).

RESULTS

We identified 126 patient episodes of MDR UTIs caused by Gram-negative bacteria treated by clinicians. These 126 patient episodes corresponded to 101 unique patients with an average age of 72.8 years. Ninety percent of the patients were male, and 85% were white. Of the 126 patient episodes, 65 (52%) episodes were treated in an acute care setting, 26 (21%) were treated in a long-term care facility, and 35 (28%) were treated in an outpatient setting.

Uropathogens. The most common uropathogen was *Escherichia coli*, present in 75/126 (60%) patient episodes, followed by *Klebsiella* species in 49/126 (39%) patient episodes and *Pseudomonas* species in 2/126 (2%) patient episodes. Overall resistance rates were 99% for third-generation cephalosporins, 84% for fluoroquinolones, 63% for trimethoprim-sulfamethoxazole, 38% for nitrofurantoin, and 2% for carbapenems.

Previous microbiologic data were available for 95 patient episodes: within 6 months for 73% of episodes and between 6 months and 2 years for 27% of episodes. A prior uropathogen of the same species as the index pathogen was identified in 78/95 (82%) episodes; in 27/95 (28%) episodes, additional uropathogens were also reported in the same or different urine samples. In 17/95 (18%) episodes, the uropathogens were completely different from the index pathogen.

Microbiologic data available within 2 years were as likely to identify the same species as the index pathogen (24/26 [92%] episodes) as microbiologic data available within 6 months (54/69 [78%]) ($P = 0.2$). there was a higher rate of agreement of the index pathogen with the prior uropathogen if the index pathogen was *E. coli* (50/55 episodes [91%]) than if the index uropathogen was *Klebsiella* (26/38 [68% episodes]) (odds ratio [OR], 4.6; 95% confidence interval [CI], 1.4 to 14.5; $P = 0.007$).

Antimicrobial therapy. Overall, the choices of empiric therapy against the index pathogen were accurate in 66/126 (52%) episodes. The most common empiric therapy chosen by the treating provider was a fluoroquinolone (32/126 [25%] episodes), followed by trimethoprim-sulfamethoxazole (23/126 [18%]), a carbapenem (18/126 [14%]), nitrofurantoin (16/126 [13%]), a nonpseudomonal beta-lactam (18/126 [14%]), an antipseudomonal beta-lactam (15/126 [12%]), and an aminoglycoside (4/126 [3%]). Fosfomycin was not chosen as empiric therapy for any episode.

Compared to the accuracy of all other antibiotic choices, broad-spectrum antibiotics (including carbapenems and antipseudomonal beta-lactams) were the most frequently accurate, covering 26/33 (78%) uropathogens. However, there was no significant difference between the accuracy of broad-spectrum agents and that of GU-directed agents, the latter of which covered 26/39 (69%) uropathogens ($P = 0.3$). The choice of a fluoroquinolone, an aminoglycoside, or a nonpseudomonal beta-lactam consistently led to inaccurate therapy, covering only 14/54 (26%) uropathogens. Neither the severity of illness, as determined by the location of empiric therapy (an inpatient, long-term care, or outpatient facility), or the year of the episode was associated with the accuracy of empiric therapy.

For the 95 patient episodes for which prior microbiologic data were available, when empiric therapy was concordant with the prior microbiologic data (even if the index event was not caused by the same species), the antibiotic covered the uropathogen in 40/52 (77%) episodes. If the empiric therapy was discordant from the prior microbiologic data, only 14/43 (33%) empiric therapy choices were accurate. The choice of an agent concordant with the prior microbiologic data was associated with a 7-fold greater chance of accuracy in treating the index infection (OR, 6.9; 95% CI, 2.7 to 17.1; $P < 0.001$).

The interval between the index episode and the episode for which prior microbiologic data were available was not associated with differences in the likelihood of accurate therapy (Table 1). However, antimicrobial therapy based on prior microbiologic data was more likely to be accurate if the prior microbiologic data indicated that the pathogen was the same species as the index

uropathogen (35/40 [88%] episodes) than if there was a shift in species (5/12 [42%]) (OR, 9.8; 95% CI, 2.2 to 43.1; $P = 0.002$).

DISCUSSION

This study demonstrates a high rate of inaccurate empiric treatment for urinary tract infections caused by MDR Gram-negative bacteria. Almost half of patients treated for an MDR UTI received an inactive antimicrobial agent as their initial therapy. An improvement in the accuracy of empiric therapy occurred when the antimicrobial was either concordant with prior microbiologic data or involved a GU-directed agent or a broad-spectrum agent, as defined by this study. However, prior microbiologic data were seemingly incorporated into clinical decision making in only about 50% of infections. A striking finding was that if previous microbiologic data were ignored, i.e., therapy for the index infection was discordant with microbiologic data obtained within the previous 2 years, the rate of accuracy of empiric therapy for the index infection dropped to 33%, an exceedingly low level in any clinical scenario.

This high rate of inaccurate treatment for MDR UTI parallels the rates found in studies evaluating the effectiveness of therapy for bacteremia caused by ESBL-producing strains, which demonstrated only 37 to 50% accuracy (6, 13). The rate of accuracy in one study improved from only 37 to 54% if the patient was a known carrier of an ESBL-producing pathogen, leading the authors to conclude that prior microbiologic data were either not consulted or neglected (13).

The utility of previous microbiologic data in choosing accurate therapy was even more robust in our study, with a 7-fold improvement in the likelihood of using accurate empiric therapy being obtained if previous microbiologic data were considered. Importantly, the utility of previous microbiologic data was demonstrated even for results obtained between 6 months and 2 years from the time of the index episode.

These data are consistent with those of a recent study in which the prior isolates were found to be highly predictive of current urinary isolates and susceptibility to ciprofloxacin (10). Our study expands upon this concept by evaluating nonfluoroquinolone antimicrobials and demonstrating improvements in the accuracy of empiric prescribing when previous microbiologic data are considered, which are key concepts for stewardship programs.

Even if prior microbiologic data are not reviewed or are not available, simply following the IDSA's guidelines for UTI treatment can improve the accuracy of prescribing, as a GU-directed agent was equally as likely to be accurate as a broad-spectrum agent, even among this cohort of patients with MDR uropathogens. The choice between these therapeutic options will likely be driven by the severity of illness, the preferred route of drug administration, and other patient factors. As our study consisted only of MDR uropathogens inherently linked with fluoroquinolone resistance, we are limited in drawing further conclusions regarding the accuracy of prescribing for this class. Nonetheless, the high rate of prescribing of fluoroquinolones is worrisome, given the high resistance rates within our cohort and demonstrated in other studies (7, 9, 10).

While additional prospective data are needed to fully validate these two simple rules, they can assist the clinician in cases where MDR uropathogens are suspected. Clearly, further clinician education regarding optimization of the accuracy of empiric treatment of UTIs is needed, and the data presented here can serve as a framework for this process.

Conclusions. Choosing an agent concordant with previous microbiologic data significantly increased the chance of accurate therapy for MDR UTIs, even if the previous uropathogen was a different species. Either GU-directed or broad-spectrum therapy choices were more likely to be accurate than other regimens. The accuracy of empiric therapy could be improved by the use of these simple rules.

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